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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/608,841	06/26/2003	Rashid A. Fawwaz	0575/66697/JPW/AJM/DNS	7635

7590 10/20/2006

Cooper and Dunham LLP
1185 Avenue of the Americas
New York, NY 10036

EXAMINER	
WEHBE, ANNE MARIE SABRINA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 10/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/608,841	FAWWAZ, RASHID A.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Applicant's response to the restriction requirement received on 8/1/06 has been entered. Applicant's election with traverse of Group I is acknowledged; however, upon further consideration, the restriction between Groups I and II is withdrawn. Therefore, claims 1-26 are currently pending and under examination in the instant application. An action on the merits follows.

Information Disclosure Statement

The applicant filed information disclosure statements(IDS) on 3/15/04, 1/6/05, and 2/3/05. These submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner, and initialed copies of the 1449s are attached to the instant action.

Specification

The disclosure is objected to because of the following informalities: the specification on page 10 line 18 refers to "Table I". However, no such Table is present in the specification as filed. This application was filed without drawings and without any Tables, Charts, or Figures.

Appropriate correction is required.

Nucleotide and/or Amino Acid Sequences

This application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Page 12 line 17 contains an amino acid sequence which meets the definition of an amino acid sequence as set forth in 37 CFR 1.821(a) and which is not identified by a SEQ ID NO. It is further noted that the applicant has not filed a paper copy and computer readable copy of the sequence listing as well as the required statement that the content of the paper and the computer readable copy are the same, see 37 CFR 1.821 (c)-(f).

Please note that the time period for response to the Notice to Comply is the same as that for the instant office action. A response to this office action must include a response to the Notice to Comply to be considered complete.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 22-23, and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Fawwaz et al. (1997) Proc. Am. Assoc. Cancer Res., Vol. 38, page 612, abstract #4110 (IDS of

2/3/05). The applicant claims a pharmaceutical composition or article of manufacture comprising/having streptavidin. While claims 23 and 25 also refer to the inclusion of packaging material with a label containing instructions for the use of the streptavidin for inhibiting transplant rejection, the applicant is reminded that where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. *In re Ngai*, F.3d, 2004 WL 1068957 (Fed. Cir. May 13, 2004) and *In re Gulack*, 703 F.2d 1381, 1385-86, 217 USPQ 401, 404 (Fed. Cir. 1983). There is no apparent functional relationship between the streptavidin and the label on the packaging material. Therefore, the label and instructions printed thereon are no given patentable weight in these product claims.

Fawwaz et al. teaches a pharmaceutical composition comprising streptavidin and the packaging of the streptavidin for intraperitoneal administration to a subject (Fawwaz et al., abstract). Thus, by teaching all the elements of the claims as written, Fawwaz et al. anticipates the instant invention as claimed.

Claims 22-26 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,861,156 (1/19/99), hereafter referred to as George et al. The applicant claims a pharmaceutical composition or article of manufacture comprising/having streptavidin. The applicant further teaches said article containing an anti-lymphocyte antibody in combination with the streptavidin. While claims 23 -26 also refer to the inclusion of packaging material with a label containing instructions for the use of the streptavidin for inhibiting transplant rejection, the applicant is reminded that where the only difference between a prior art product and a claimed product is

printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. *In re Ngai*, F.3d, 2004 WL 1068957 (Fed. Cir. May 13, 2004) and *In re Gulack*, 703 F.2d 1381, 1385-86, 217 USPQ 401, 404 (Fed. Cir. 1983). There is no apparent functional relationship between the streptavidin and/or anti-lymphocyte antibody and the label on the packaging material. Therefore, the label and instructions printed thereon are no given patentable weight in these product claims.

George et al. teaches binding proteins for delivering an agent to a target cell in methods of immunotherapy (George et al., abstract, and column 3). Specification, George teaches the delivery of a first monospecific binding protein tagged with a peptide for binding to a target cell and a second multivalent antibody which binds to the tagged target cell and to a cytotoxic agent or cytotoxic T cell (George et al, columns 3-4). In a specific embodiment, George et al. teaches that the multivalent antibody is streptavidin tagged anti-CD3 antibody (George et al., column 10, column 5). As CD3 is expressed on T lymphocytes, the anti-CD3 antibody is an anti-lymphocyte antibody. Thus, by teaching all the elements of the claims as written, George et al. anticipates the instant invention as claimed.

Claims 1, 22-23, and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,328,985 (7/12/94), hereafter referred to as Sano et al. The applicant claims a method for inhibiting the immunological rejection of a transplant comprising administering a prophylactically effective amount of streptavidin, and a pharmaceutical composition or article of manufacture comprising/having streptavidin. While claims 23 and 25 also refer to the inclusion of packaging material with a label containing instructions for the use of the streptavidin for

inhibiting transplant rejection, the applicant is reminded that where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. *In re Ngai*, F.3d, 2004 WL 1068957 (Fed. Cir. May 13, 2004) and *In re Gulack*, 703 F.2d 1381, 1385-86, 217 USPQ 401, 404 (Fed. Cir. 1983). There is no apparent functional relationship between the streptavidin and the label on the packaging material. Therefore, the label and instructions printed thereon are no given patentable weight in these product claims.

Sano et al. teaches a recombinant streptavidin-Protein A chimeric protein and the use of this protein for the prevention or treatment of infection in transplant recipients (Sano et al., columns 4-5, and columns 17-18, especially column 17, lines 7-21). While Sano et al. does not teach that the purpose of administering the chimeric streptavidin protein is for inhibiting transplant rejection, it is a general rule that merely discovering and claiming a new benefit to an old process cannot render the process again patentable. *In re Woodruff*, 919 F. 2d 1575, 1577-78, 16 USPQ2d 1934, 1936-37 (Fed.Cir. 1990); *In re Swinehart*, 439 F.2d 210, 213, 169 USPQ 226, 229 (CCPA 1971); and *Ex Parte Novitski*, 26 USPQ2d 1389, 1391 (Bd. Pat. App. & Int. 1993). The MPEP also states that "when the claim recites using an old composition or structure and the 'use' is directed to a result or property of that composition or structure, then the claim is anticipated. *In re May*, 574 F. 2d 1082, 1090, 197 USPQ 601, 607 (CCPA 1978)". MPEP 2112.02. Sano et al. teaches the same method steps as the instant method, including administration to a transplant recipient. As such, Sano et al. anticipates the instant invention as claimed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of delaying the rejection of an allograft in a subject comprising transplanting an allogeneic tissue or organ to a subject and administering by intraperitoneal injection 20 mg/kg of streptavidin for five consecutive days starting on the day of transplant, does not reasonably provide enablement for inhibiting the rejection of any transplant, and in particular a xenogenic transplant, comprising administering at any time before or after transplantation of an organ, tissue, or cells, an amount of streptavidin using any route of administration, including intravenous or subcutaneous. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Please note that claims 22-26 are included in this rejection based on their intended use as recited either in the claim itself, or in the specification as filed.

The claims read broadly on the inhibition of transplant rejection of any type of organs, tissues, or cells, including syngeneic, allogeneic, or xenogeneic cells/tissues/organs. However, while the specification contemplates using streptavidin to inhibit xenograft rejection, the specification is primarily directed to reducing the incidence of cardiac allograft rejection in rats and provides no specific guidance for preventing xenograft rejection in any species using

streptavidin or a combination of streptavidin and an anti-lymphocyte antibody. In addition, it is noted that the working examples present in the specification deal exclusively with allogeneic transplantation. While the working examples demonstrate that the intraperitoneal administration of 20mg/kg of streptavidin for five consecutive days starting on the day of cardiac allograft transplantation in rats significantly delays graft rejection, the results of the working examples cannot be predictably extrapolated to delaying or inhibiting xenograft rejection. The transplantation literature teaches that hyperacute rejection due to the presence of pre-existing anti-xenogeneic antibodies is a major barrier to successful xenotransplantation (Kaufman et al. (1995) Annu. Rev. Immunol., Vol. 13, pages 342-343). Further, in a transplant setting where xenoantibodies are absent or are inhibited by antisera, rejection still occurs through alternative complement, T cell, and NK cell mediated mechanisms (Kaufman et al. (1995) whole document). In particular, cytokines secreted from xeno or allo-activated T cells, especially CD4+ T cells, mediate inflammatory destruction of graft tissue. Prevention of rejection in xenotransplants and allografts requires inhibition or suppression of multiple components of both the immune and inflammatory responses. According to Kaufman et al. in their review of the field of xenotransplantation, " In experimental and clinical protocols in which immunosuppressive agents ... were administered to recipients of xenografts, vigorous rejection occurred , even when profoundly immunosuppressive combinations of agents were utilized, " and that, " Short term prolongation of graft survival has been achieved by a number of methods, none of which appears to be clinically feasible at this time" (Kaufman et al. (1995), page 347, lines 18-20, and 29-32). Thus, the prior art establishes that while rejection of both allogeneic and xenogeneic tissue occurs through the activity of multiple components of the immune system, xenogeneic rejection

is particularly difficult to inhibit due to the presence of preformed antibodies whose activity is not affected by even profoundly immunosuppressive combinations of agents. As such, the skilled artisan would not have been able to predictably correlate success in delaying allograft rejection with success in delaying xenograft rejection. Therefore, due to the states of the art of xenotransplantation, the differences between xenograft rejection and allograft rejection, the lack of specific guidance for preventing/inhibiting xenograft rejection using streptavidin, the limitation of the working examples to delaying cardiac allograft rejection, and the breadth of the claims, it would have required undue experimentation to practice the scope of the invention as claimed.

In addition, the specification teaches on page 2 that there is no known nexus between streptavidin and the inhibition of immunological rejection, and later states on page 12 that the underlying mechanisms of graft prolongation by streptavidin has not yet been determined. At the time of filing, streptavidin was commonly used as a binding partner for biotin in a variety of applications ranging from in vitro assays to in vivo diagnostics and therapy. The applicant previously published work demonstrated that intraperitoneal administration of streptavidin was capable of a statistically significant antiproliferative effect on a human breast cancer xenograft in nude mice. However, none of the prior art references of record demonstrate that streptavidin is capable of having any type of effect on any immune effector cell, including T cells, or B cells *in vitro* or *in vivo*. In fact, the prior art contains numerous teachings for the use of streptavidin in various immunoconjugates for the purpose of stimulating an immune response through targeting of immune effector cells to various cells of interest. See for instance U.S. Patents 5,861,156 and 5,328,985 cited above. Thus, the applicant's working examples provide a single example of

conditions under which streptavidin is apparently capable of delaying allograft rejection. These conditions include the intraperitoneal injection of the streptavidin and a dosage regimen of 20 mg/kg for 5 days starting on the day of transplant. While the specification contemplates other embodiments, including intravenous or subcutaneous administration, and the administration of a single dose of streptavidin from 2 mg/kg to 200 mg/kg, the applicant's working examples provides no demonstration that any conditions other than those actually tested can achieve any effect on allograft rejection.

Further, the claims as written broadly recite that the streptavidin is administered "at a suitable time" to inhibit immunological rejection. The specification on page 5 defines a "suitable time" as "any time at which streptavidin administered would be expected to inhibit the immunological rejection of the transplant". The definition goes on to give some preferred examples, including within one or two days prior, on, or one to five days after transplant, but stresses that a "suitable time" is not limited to these particular times. However, aside from the administration of streptavidin from days one to five post transplant, the specification fails to provide any specific guidance that single of multiple administrations of streptavidin at any other time points can have any effect on graft rejection. It is particularly noted that the rejection of third party allografts transplanted 60 days after a 5 day course of streptavidin did not differ from untreated controls. Thus, the specification fails to provide sufficient guidance as to any "suitable time" for streptavidin administration other than administration on days 1-5 post transplant.

Therefore, given the extensive body of literature concerning the activity and use of streptavidin both *in vitro* and *in vivo*, including the use of streptavidin in methods of immunostimulation, the state of the art of allograft and xenograft transplantation as taught by

Kaufman, the single example of conditions under which streptavidin is capable of affecting allograft rejection, and the breadth of the claims, it would have required undue experimentation to test all the various parameters involved in the instant methods to find alternative conditions under which streptavidin would inhibit graft rejection. Thus, the specification is only enabling for methods of delaying the rejection of an allograft in a subject comprising transplanting an allogeneic tissue or organ to a subject and administering by intraperitoneal injection 20 mg/kg of streptavidin for five consecutive days starting on the day of transplant

No claims are allowed.

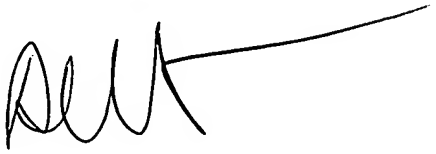
Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your

application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER



Application No.: 10/608,841

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [ ] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [ ] 7. Other:

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

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